Eon Labs
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.
227-15 N. Conduit Avenue
Laurelton, NY 11413
Telephone 718 276-8600
Fax 718 276-1735

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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

RE: Docket #01P-0585 -- Citizen Petition
ANDA for mixed salts of single entity amphetamine, Adderall®

On behalf of Eon Labs Manufacturing, Inc. I would like to respond to the Citizen Petition (Docket #01P-0585) concerning applicants of an abbreviated new drug application (ANDA) for mixed salts of a single entity amphetamine product. The Citizen Petition submitted by Arnall Golden Gregory, LLP wrongly implies that ANDA approval of a generic drug product for Adderall® would allow for the marketing of a drug product that may be less safe and have more substance abuse potential. We strongly feel that this Citizen Petition should be denied. The Citizen Petition lacks merit and the current FDA review standards for ANDA submissions adequately provide for the marketing of therapeutically equivalent generic drug products that have the same safety and efficacy profile as the reference listed drug product (RLD).

The Citizen Petition requests, "*that the Commissioner require an applicant for an ANDA of mixed salts of a single entity amphetamine product to conduct the necessary testing, including assessment of bioequivalence, to assure strict equivalence with key pharmacokinetic parameters of the RLD, Adderall®, so that the safety profile, including dependence and abuse characteristic of the ANDA are the same as the RLD.*"

FDA review and approval process for ANDA submissions

The issues raised by the Citizen Petition are considered by FDA during the review and approval process for generic drugs. The FDA process for generic drug product approval was formally developed by the FDA with the input of expert advisory committees. The FDA has rigid guidelines developed over a 16 year period, for the approval of therapeutic equivalent drug products. The FDA thoroughly reviews the Sponsors' application and audits its facilities and applies the same quality standards to generic drug products as they do for new drug products. FDA approval includes an assurance that the

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generic drug product is safe, efficacious and may be safely substituted for the branded product to provide the same clinical effectiveness. The FDA should not change its review and approval process for an ANDA submission for a generic equivalent to Adderall®.

Abuse potential

The Citizen Petition discusses the abuse potential of stimulant medications. This fact is well described in the literature. However, none of the references in the Citizen Petition provide clinical data for the abuse potential of Adderall® in terms of the rate of oral drug absorption. The Citizen Petition does not provide evidence that a small difference in the rate of systemic amphetamine absorption from Adderall® would lead to differences in substance abuse potential or safety.

Indeed, I am well aware of substance abuse liability and have discussed this issue in my textbook[1]. I agree that the rate of systemic drug absorption has been associated with the potential for drug abuse. However, drugs taken by the oral route have the lowest potential for substance abuse. Substance abusers generally prefer to change the route of administration to obtain more rapid absorption. For example, chewing of cocoa leaves containing cocaine have much less abuse potential than smoking 'crack' cocaine. Within a drug class (e.g., methamphetamine versus amphetamine, heroine versus codeine), the more rapidly absorbed drug has the greater substance abuse potential.

The Citizen Petition also states without clinical evidence that, "*although conventional pharmacokinetic parameters do not correlate with the kinetics of reinforcement described here, the slope of the early rise in plasma concentration and the early partial AUC may provide an indication of the dependence risk and be additional tools in setting acceptable ranges for bioequivalence for this special class of medications.*"

Generic drug products are pharmaceutical equivalents that contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration[2]. For FDA approval of a generic drug product, the conventional criteria for bioequivalence is based on 90% confidence intervals for Cmax and AUC as metrics for the rate and extent of systemic drug absorption, respectively. The demonstration of bioequivalence of a generic drug product to the RLD would preclude any significant difference in oral drug absorption, abuse potential or safety.

Adderall® should not be considered as a "*special class of medications*" in terms of generic drug development. Many generic drug products that have substance abuse potential have been approved by the FDA based on the accepted standards for bioequivalence. Some examples include, opiates (e.g., pentazocine hydrochloride),

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[1] Shargel L, Yu ABC, *Applied Biopharmaceutics and Pharmacokinetics*, 4th edition, McGraw-Hill, 1999, pp 584-585. See also, Hardman JG, Limbird LE (ed), Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th edition, McGraw-Hill, 2001, Chapter 24,

[2] Approved Drug Products with Therapeutic Equivalence Evaluations ('Orange Book"), http://www.fda.gov/cder/ob

benzodiazepines (e.g., lorazepam), and stimulants (e.g., methylphenidate hydrochloride). All of these generic products may be safely substituted for their brand name equivalent.

The Citizen Petition also states, "*Preferably the ANDA applicant should provide comparative clinical evidence showing that the product's safety profile is the same as that of the RLD.*"

The Drug Price Competition and Term Restoration Act of 1984 (Waxman – Hatch Act) established a process for the ANDA. The ANDA is based on bioequivalence to the brand name product, appropriate chemistry and manufacturing information and appropriate labeling. According to the Act, sponsors do not have to duplicate the non-clinical animal toxicity studies nor expensive clinical efficacy and safety studies that are included in the new drug application (NDA). As stated in the Orange Book and elsewhere[3], "*FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.*"

In summary, the Citizen Petition should be denied. The petition has not provided any data that shows that the current FDA review and approval process for a generic version of Adderall® would lead to a less safe product with more abuse potential. The references in this petition contain a general information on substance abuse liability that appears in many textbooks. Adderall® is not in a *special class of medications* that should be treated any differently from other solid oral dosage form in terms of an ANDA approval. Comparative clinical evidence for this product is unnecessary and unwarranted

I appreciate your consideration of my comments and would be happy to answer any questions.

Yours truly,

Leon Shargel

Leon Shargel, Ph.D., R.Ph.
Vice President, Biopharmaceutics

cc: Mr. Gary Buehler, Office of Generic Drugs, FDA

[3] Stuart L. Nightingale, M.D. Associate Commissioner for Health Affairs, FDA, *Therapeutic Equivalence of Generic Drugs*, Letter to Health Practitioners, 1/28/98; Roger L. Williams, M.D., Deputy Center Director for Pharmaceutical Science Center for Drug Evaluation and Research, FDA, *Therapeutic Equivalence of Generic Drugs*, Response to National Association of Boards of Pharmacy, 4/16/97

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